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Review

MLL fusions

Pathways to leukemia

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Abbreviations: MLL, mixed lineage leukemia or myeloid lymphoid leukemia; HRX, human trithorax; ALL-1, acute lymphoblastic leukemia 1; GMP, granulocytic/monocytic-restricted progenitors; CB, cord blood; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; ABL, acute biphenotypic leukemia; MPD, myeloproliferative disorder; HMT, histone methyltransferase; HAT, histone acetyltransferase

Key words: MLL, mixed lineage leukemia, MLL fusions, 11q23 translocation, Hox, cell cycle, cell fate, taspase1

Human leukemias with chromosomal band 11q23 aberrations that disrupt the *MLL/HRX/ALL-1* gene portend poor prognosis.¹⁻¹³ MLL associated leukemias account for the majority of infant leukemia, ~10% of adult de novo leukemia and ~33% of therapy related acute leukemia with a balanced chromosome translocation. The 500 kD MLL precursor is processed by Taspase1 to generate mature MLL^{N320/C180}, which orchestrates many aspects of biology such as embryogenesis, cell cycle, cell fate and stem cell maintenance. Leukemogenic MLL translocations fuse the common MLL N-terminus (~1,400 aa) in frame with more than 60 translocation partner genes (TPGs). Recent studies on MLL and MLL leukemia have greatly advanced our knowledge concerning the normal function of MLL and its deregulation in leukemogenesis. Here, we summarize the critical biological and pathological activities of MLL and MLL fusions, and discuss available models and potential therapeutic targets of MLL associated leukemias.

The MLL Leukemia

Human leukemias with an MLL translocation account for >50% of acute lymphoblastic leukemia (ALL) in infants less than 6 months of age and for up to 10% of both de novo acute lymphoblastic and acute myeloid leukemia (AML) in children and adults.¹⁴ Furthermore, MLL translocations are also observed in ~33% of therapy-related myelodysplastic syndromes or acute leukemia patients with balanced chromosome aberrations.¹⁵ MLL stands for Mixed Lineage Leukemia or Myeloid Lymphoid Leukemia as leukemic blasts of MLL-associated leukemia commonly express both lymphoid and myeloid markers, and MLL translocations

can result in both ALL and AML, respectively. The biphenotypic surface expression of these blasts has led to a proposal that 11q23 abnormalities transform a hematopoietic stem/progenitor cell. Based on gene expression profiles, acute leukemia possessing a rearranged *MLL* exhibits a highly uniform and distinct pattern that clearly distinguishes them from conventional ALL or AML.¹⁶⁻¹⁸

The Discovery of MLL (MLL1/HRX/ALL-1)

Discovered in 1992 from cloning the gene that is disrupted in human 11q23 leukemias,^{19,20} the *MLL/HRX/ALL-1* (subsequently assigned as *MLL1*) gene has since attracted scientists from various disciplines by its diverse functions in normal physiological and pathological processes.

MLL was shown to be the mammalian counterpart of *Drosophila trithorax (trx)*, the founder of trithorax group (Trx-G) genes.¹⁹⁻²⁴ Genetic evidence indicated that trithorax group (Trx-G) proteins antagonize with polycomb group (Pc-G) proteins for proper *homeotic* gene expression through chromatin modifications.²⁵⁻²⁷ As a transcription coactivator, MLL/trx is required for the maintenance of spatial patterns of *Hox* and *HOM-C* (*homeotic complex*) gene expression in vertebrates and invertebrates, respectively. Homozygous deficiency for *MLL* results in early embryonic lethality at embryonic day 10.5 (E10.5), while heterozygous deletion of *MLL* incurs homeotic transformation, indicating altered *Hox* gene expression.²⁸⁻³⁰ Of note, five MLL family proteins, i.e., MLL1-5, have been identified but only MLL1 is involved in human leukemias.³¹

The MLL Protein

MLL orchestrates essential biological processes through its architecturally positioned domains that bind DNA either directly (sequences enriched for AT rich or non-methylated CpG) or indirectly (through sequence specific transcription factors such as E2Fs), provide interfaces for the assembly of multi-protein complexes, and methylate histone H3 at lysine 4. In brief, the *MLL* gene encodes a 3,969 amino acid, 500 kD protein with

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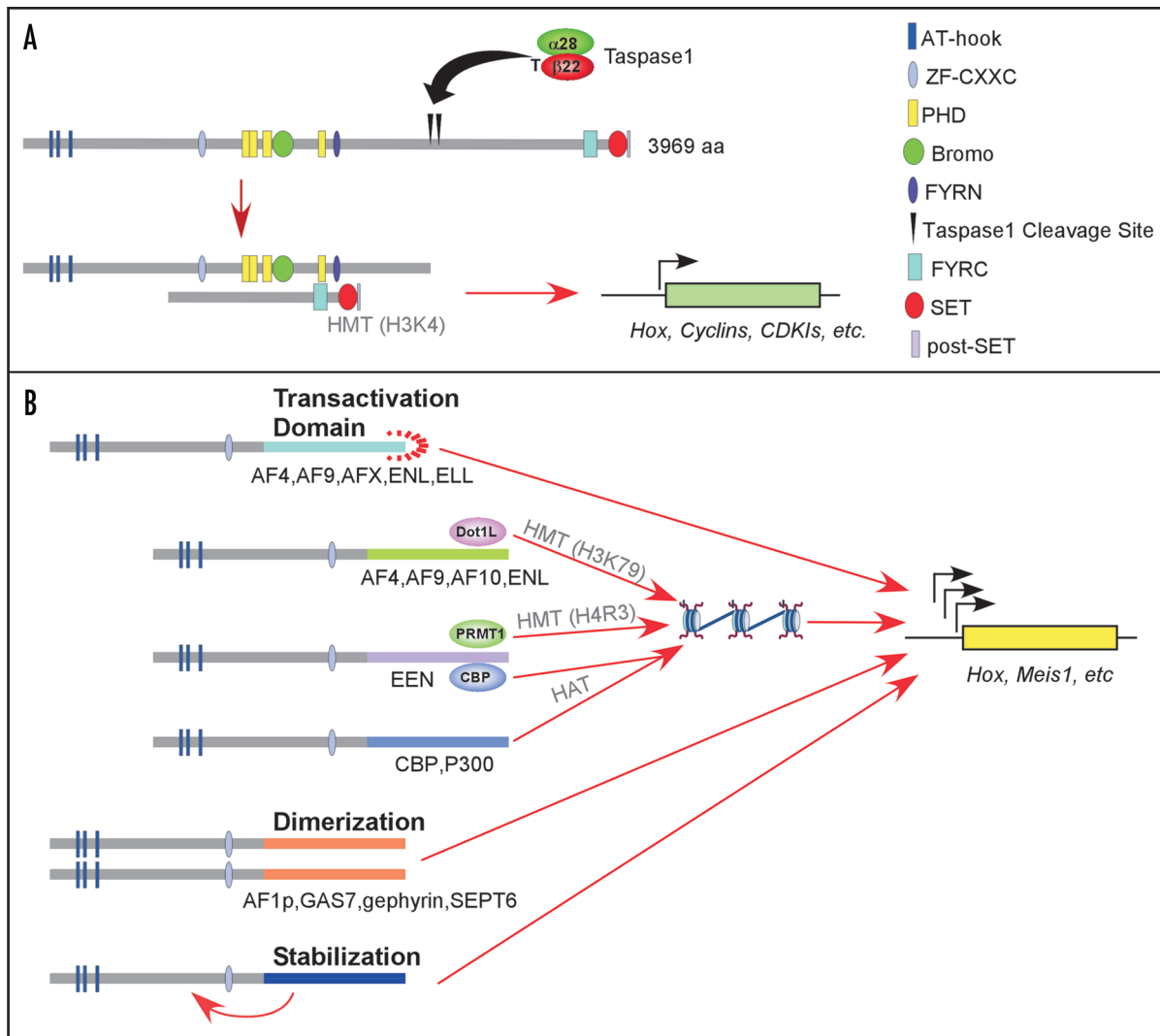


Figure 1. (A) Domain structure and the proteolytic maturation of the MLL protein. (B) Mechanisms of MLL fusion induced gene deregulation.

multiple conserved domains of distinct functions: (1) three AT hooks, found near the N-terminus of MLL, mediate its binding to the minor groove of AT-rich DNA region.³² (2) a transcription repression domain consists of a cysteine-rich CXXC DNMT (DNA methyltransferase1) homology region³³ that can binds non-methylated CpG.³⁴ (3) four PHD fingers mediate protein-protein interactions.³⁵ (4) a transactivation domain interacts with CBP/P300.³⁶ (5) a C-terminal SET domain functions as a histone methyl transferase (HMT) that methylates Histone H3 at K4, marking transcriptionally active genes (Fig. 1A).^{37,38} Over the years, a plethora of MLL interaction partners have been identified, providing mechanistic insights regarding how MLL regulates complex gene expression. MLL forms complexes with Menin (a tumor suppressor),^{39,40} cell cycle regulators (E2Fs and HCF-1),⁴⁰⁻⁴² Pc-G proteins (BMI-1 and HPC2),³³ HDACs (Histone Deacetylases),³⁸ Cyp33 (a nuclear cyclophilin),³³ CBP/P300 and MOF (histone acetyltransferase),^{36,43} INI1/SNF5 (chromatin remodeling factors)⁴⁴ and core components of the H3K4 histone methyl transferase (WDR5, RbBP5 and Ash2L).^{45,46} In

addition to the aforementioned complexity of MLL gene regulation, we and others showed that the full length MLL precursor (MLL^{FL}) undergoes evolutionarily conserved site-specific proteolysis by Taspase1 to generate the mature MLL^{N320/C180} consisting of processed N-terminal 320 kD (MLL^{N320}) and C-terminal 180 kD fragments (MLL^{C180}).^{38,47,48} that heterodimerize through the FYRN domain of MLL^{N320} and the FYRC plus SET domains of MLL^{C180}. Taspase1-mediated cleavage of MLL is an evolutionarily conserved regulatory event that enables the spatiotemporal control of MLL downstream targets.⁴¹

The MLL Biology

The best characterized function of MLL is maintaining the expression of *Hox* clusters that dictate cell fate. The 39 mammalian *HoxA-D* genes encode highly conserved homeobox containing transcription factors of which the combinatorial expression confers the identity of individual body segments and regulates hematopoiesis. Besides regulating cell fates, it is evident that MLL also orchestrates cell cycle progression at least through regulating

the expression of cyclins and CDK inhibitors (CDKIs).^{41,49-51} Interestingly, the positive and negative influence of MLL on the cell cycle is context dependent and involves its HMT activity. Furthermore, MLL itself is regulated by the cell cycle machinery. MLL undergoes a specialized bimodal degradation resulting in its biphasic expression through the cell cycle.⁵² This unique expression is conferred by SCF^{Skp2} and APC^{Cdc20}, two cell cycle specific E3 ligases. Importantly, deregulation of this highly choreographed expression through either overexpression or knockdown incurs cell cycle defects. The ability of MLL in coordinating cell fate and cell cycle regulation help to explain its essential role in both hematopoietic and neuronal stem cells.⁵³⁻⁵⁵

Mouse Models of the MLL-Associated Leukemia

To investigate the aetiology, pathogenesis, progression and response to treatment, several mouse models have been engineered to recapitulate individual MLL associated leukemias. The first successful MLL leukemia model in mice employed the MLL-AF9 knock-in allele in which the *AF9* sequence was integrated into one of the endogenous *MLL* allele via homologous recombination in mouse embryonic stem cells (ES cells), leaving the other *MLL* allele as wild-type.⁵⁶ The MLL-AF9 knock-in mice developed an acute myeloid malignancy similar to what occurs in human patients with the chromosomal translocation t(9;11). Similar knock-in approaches were used to investigate the role of MLL-AF4 and MLL-PTD (partial tandem duplication) in leukemia.^{57,58}

Although the knock-in approach closely mimic the naturally occurring chromosomal translocations, it is limited by the fact that some of the knock-in alleles such as MLL-CBP result in embryonic lethality.⁵⁹ Accordingly, mice bearing conditional MLL-CBP knock-in allele were generated. The conditional MLL-CBP allele consists of a stop cassette flanked by loxP sites that is inserted 5' to the CBP fusion. Before cre-mediated excision of the inserted stop cassette, the MLL-stop-CBP allele expresses truncated form of MLL. Upon excision of the stop cassette, the MLL-CBP fusion is specifically induced which mimics the human t(11;16) MLL-CBP leukemia. The induction of MLL-CBP results in an expansion of myeloid precursors in mice and these preleukemia mice only developed AML following the administration of sub-oncogenic doses of genotoxins.⁵⁹ A similar strategy was used to generate a conditional MLL-AF4 knock-in mouse model.⁶⁰ An alternative approach termed the invertor method was used to generate a mouse model of the MLL-AF4 fusion. The invertor conditional knock-in method depends on gene targeting of an inverted cDNA floxed cassette comprising a short intron, an acceptor splice site, an *AF4* cDNA segment and a polyadenylation (pA) sequence, into the intron of *MLL* gene. The cassette is in the opposite orientation of transcription to the target gene until inverted by Cre recombinase.⁶¹

To perfect MLL leukemia models in mice, an elegant chromosome translocator approach was invented. The de novo creation of chromosomal translocation recapitulates the naturally occurring balanced translocation between MLL and its translocation partner gene (TPG), which is achieved by inserting one loxP site into the common breakpoint region of *MLL* and the other into the TPG. The MLL-TPG and TPG-MLL alleles are generated in

vivo upon cre-mediated recombination. Forster et al. established a line of mice in which cre recombinase was regulated under the hematopoietic Lmo2 promoter and loxP sites were placed in the *MLL* and *ENL* loci.⁶² The Cre-loxP-mediated interchromosomal recombination between the *MLL* and *ENL* genes creates reciprocal chromosomal translocations, which rapidly causes myeloid tumors with rapid onset and high penetrance. The same system was utilized to assess the MLL-AF9 leukemia.⁶³ The translocator mice models are the closest to natural chromosomal translocations in human cancers, as both derivative chromosomes are created somatically. However, this strategy requires that both targeted genes on the relevant mouse chromosomes are transcriptionally orientated into the directions of telomeres to generate the correct fusion following translocation. Therefore, this approach can't apply to certain MLL fusions such as MLL-AF4.

Retroviral transduction of BM cells with MLL fusion genes followed by transplantation into syngeneic recipient mice is widely utilized to model MLL-associated leukemia. Such an approach provides quick assessments of individual MLL fusions in leukemogenesis and enables structure-function analysis to investigate which domain and what activity of MLL fusion is required for oncogenic transformation.^{64,65} These studies have generated invaluable insights regarding the underlying mechanisms by which MLL fusions cause human leukemia. However, the employment of retroviruses likely results in uncontrolled, nonphysiological expression of MLL fusions. The importance of gene dosage in MLL leukemogenesis has been recently demonstrated using MLL-AF9.⁶⁶ Furthermore, random insertion of retroviruses is known to facilitate oncogenesis through activation of an oncogene and/or inactivation of a tumor suppressor gene. Therefore, the retroviral strategy generally results in leukemias with shorter latencies compared to the knock-in approach. Importantly, retrovirus-mediated MLL fusion gene transfer into murine bone marrow cells demonstrated that both hematopoietic stem and more differentiated progenitor cells can be successfully transformed to induce leukaemia.⁶⁷ Using a similar retroviral strategy, MLL-ENL and MLL-AF9 were shown to be capable of transforming primary human hematopoietic cells in a tumor xenograft model. In this study, MLL-ENL induces acute B-lymphocytic leukemia (B-ALL).⁶⁸ The current mice models for MLL leukemias are summarised in Table 1.

Molecular Models of MLL-Associated Leukemia

The most fascinating feature of MLL associated leukemia is the unprecedented diversity of TPGs. To date, 104 different MLL rearrangements have been described and of which 64 TPGs are characterized at the molecular level.⁶⁹ Leukemogenic 11q23 translocations fuse the common MLL N-terminal 1,400 aa in-frame with a wide variety of fusion partners (>60) that ranges from nuclear factors to cytoplasmic proteins. Accumulative studies have now yielded major breakthroughs in our understanding of MLL associated leukemia.

Genetic studies on mice carrying individual MLL fusions reveal several fundamental aspects concerning MLL associated leukemia. First, MLL fusions, the products of 11q23 translocations, are responsible for the leukemogenesis.^{56,57,59,70,71} Second,

Table 1 Mouse models of MLL associated leukemias

MLL fusion	Model	Phenotype	Latency (months)	Reference
MLL-AF4	knockin	lymphoid/myeloid hyperplasia, B-cell lymphoma	17	57
	conditional knockin/Mx1-Cre	B-ALL, AML	4	60
	conditional knockin, inverter/Rag, Lck, CD19-Cre	B-cell lymphoma	15	61
MLL-AF9	knockin	AML, MPD-like myeloid leukemia	7	56, 57
	translocator/Lmo2-Cre	MPD-like myeloid leukemia	9	63, 112
	retroviral	AML	3	67
	retroviral/GMP	AML	2	95
	retroviral/Human CB, Lin ⁻	B-ALL, AML, MLL	4	68
	retroviral/Human CB, CD34 ⁺	AML, B-ALL, ABL	2	113
MLL-ENL	retroviral/Human CB, Lin ⁻	B-ALL	4	68
	translocator/Lmo2-Cre	MPD-like myeloid leukemia	3	62
	translocator/Lck-Cre	T-cell lymphoma, myeloid leukemia	17	112
	retroviral	AML	3	64
MLL-ELL	retroviral	AML	5	114
MLL-AF10	retroviral	AML	3	115, 116
MLL-AF1p	retroviral	myeloid leukemia	3	74
MLL-AFX	retroviral	AML	7	73, 116
MLL-FKHRL1	retroviral	AML	5	116
MLL-SEPT6	retroviral	MPD	4	85
MLL-GAS7	retroviral	MLL	3	74, 117
MLL-EEN	knockin	myeloid leukemia	8	118
MLL-CBP	conditional knockin	myeloid hyperplasia	NA	59
	retroviral	myeloid leukemia	5	119
MLL-PTD	knockin	viable	NA	58

fusion partners are indispensable.⁷² Third, fusion partners can be as non-specific as bacterial galactosidase (*lacZ*) in that mice bearing *MLL-lacZ* developed myeloid leukemias after a prolonged latency.⁷² Fourth, individual fusion partners determine the phenotypes of resulting leukemias. For example, mice carrying *MLL-AF4* or *MLL-AF9* develop lymphoid versus myeloid malignancies, mimicking human counterparts.^{57,61,70} Detailed analyses of individual MLL fusions have established two prevalent models, transactivation and dimerization, emphasizing the gain-of-function of *Hox* gene expression and thus the disruption of blood lineage commitment.^{65,73-75} All of the 11q23 translocations truncate MLL, which result in the invariable loss of the PHD fingers, the Taspase1 cleavage sites, the transactivation domain, and the SET domain. Nevertheless, MLL fusion proteins retain the ability to target and activate *Hox* genes.

Several studies have shown that MLL fusion partners are involved in transcription initiation and elongation. For example, the most common MLL fusion partners AF4, AF9 and ENL contain transcriptional activation domains, while ELL is an elongation factor that associates with RNA polymerase II.⁷⁶ In the case of ENL, ELL and AFX, their transcriptional activation domain appears to be crucial for oncogenesis.^{65,73,77} The activation of target genes by MLL fusions can also be mediated through histone modifications

other than H3K4 methylation: (1) CBP and p300, fusion partners of MLL, are histone acetyl transferases, (2) MLL-AF10 and MLL-ENL recruit DOT1L and promote of histone H3 lysine 79 (H3K79) methylation on the *HoxA9* promoter.⁷⁸⁻⁸⁰ Remarkably, other MLL fusion partners such as AF4 and AF9 also interact with DOT1L.^{81,82} (3) MLL-EEN recruits CBP and protein arginine methyl transferase (PRMT1) to MLL target genes.⁸³ Taken together, convincing evidence highlights deregulated histone modification as an important mechanism whereby MLL fusion induces leukemia (Fig. 1B).⁸³

The second prevalent model concerning MLL associated leukemia entails the forced dimerization of the MLL N-terminus retained in all MLL fusions. The oligomerization domains of AF1p, GAS7, gephyrin and SEPT6 proteins are necessary and sufficient for leukemogenic transformation induced by the respective MLL fusion proteins.^{74,84,85} Dimerization of MLL-FKBP fusion protein, which dimerizes only in the presence of the dimerizer, AP20187, immortalizes hematopoietic cells and imposes a reversible block on myeloid differentiation.⁷⁵ The transactivation and dimerization models are not mutually exclusive since the forced dimerization of MLL was proposed to initiate a transactivation complex capable of stimulating *Hox* expression in the absence of H3K4 methylation. As mice bearing *MLL-lacZ* developed leukemias, it has been

postulated that lacZ induces leukemias through either oligomerizing or stabilizing the leukemia initiating MLL N-terminus.⁷² The MLL degradation signals lies in its N-terminal 1,400 aa which is universally retained in MLL fusions. Importantly, the prevalent MLL-Fusions, as well as MLL-lacZ, are relatively resistant to degradation mediated by the cell cycle specific E3 ligases,⁵² which constitutes a functional commonality among structurally diversified fusion partners. The predicted loss of the biphasic expression of MLL fusions may represent a common mechanism that is mechanistically compatible with the transactivation and dimerization models (Fig. 1B).

Key Target Genes and Pathways of MLL-Associated Leukemia

Gene expression profiling demonstrated a characteristic gene expression pattern for leukemias with MLL rearrangements. A common unifying feature in MLL leukemias is the extremely high expression of *Hox* genes, especially the 5'-*HoxA* cluster genes including *HoxA5-11*.¹⁶⁻¹⁸ Deregulation of *HoxA* cluster genes has been demonstrated to play a critical role in many MLL leukemias, e.g., transformation of myeloid progenitors by MLL-ENL is dependent on *HoxA7* and *HoxA9*.⁸⁶ However, not all MLL fusions solely depend on *Hox* genes for leukemogenesis. For example, though *HoxA7* and *HoxA9* affect disease latency, penetrance and phenotypes, they are not necessary for MLL-GAS7 mediated leukemogenesis.⁸⁷ Similarly, *HoxA9* affects the overall survival and the leukemia phenotype, but not the disease incidence in mice bearing knock-in allele of *MLL-AF9*.^{88,89} Furthermore, microarray analysis of human leukemias with MLL-PTD did not reveal a characteristic signature with altered *Hox* gene expression.⁹⁰ Thus, it is likely that deregulation of critical pathways, other than *Hox* genes, are of significance in MLL leukemias.

Besides *Hox* genes, other genes and signaling pathways are shown to associate with MLL leukemias and thus provide additional therapeutic targets. (1) MLL leukemias also exhibit high expression of another homeobox gene, *Meis1*; the importance of which for MLL-rearranged leukemias has been demonstrated.^{91,92} Further study shows c-Myb is not only an essential target for *HoxA9/Meis1* mediated transformation,⁹³ but also a critical component of the program for *HoxA/Meis*-independent immortalization of myeloid progenitors.⁹⁴ Other important target genes include but are not limited to *p27*,⁵⁰ *Mef2c*⁹⁵ and *EphA7*.⁹⁶ (2) The activity of the small GTPase protein, Rac1, is upregulated in murine cells expressing MLL-AF9.⁶⁷ Subsequent studies showed that the Rac signaling pathway regulates MLL associated leukemia and treatment with a Rac inhibitor or genetic ablation of Rac induces cell cycle arrest and apoptosis in these leukemia cells.⁶⁶ (3) FLT3, a class III receptor tyrosine kinase that shares structural similarity with c-Kit, and PDGFR, plays an important role in early hematopoietic development and is consistently overexpressed in MLL leukemias. Accordingly, FLT3 inhibitors are active against MLL associated leukemia in a tumor xenograft model.⁹⁷ (4) Using a pharmacological screen, a recent study demonstrated that selective inhibitors of GSK-3 specifically inhibited the growth of human MLL leukemia but not other leukemia cells.⁹⁸ (5) Menin forms a

complex with a conserved region of the N terminus of MLL that is retained in all oncogenic MLL fusion proteins.⁹⁹ Menin is a tumor suppressor whose loss of function causes human multiple endocrine neoplasia. Counterintuitively, Menin apparently serves as an essential oncogenic cofactor for MLL oncoproteins in leukemic transformation.¹⁰⁰

Distinct microRNA expression profiles were identified in MLL leukemias.^{101,102} MicroRNAs (miRNAs) are short 20- to 22-nt RNAs that negatively regulate gene expression at the posttranscriptional level by base-pairing to the 3'-UTR of target messenger RNAs. The *mir-17-92* cluster in particular, is overexpressed in human AMLs with MLL rearrangement.¹⁰³ Additional miRNAs, such as *mir-191*, are deregulated in leukemic cell lines bearing MLL rearrangements.¹⁰⁴ Moreover, overexpression of *mir-196b* by MLL fusions contributes to MLL fusion-mediated immortalization.¹⁰⁵

Perspectives

Over the past decade, we have witnessed the remarkable strides made towards understanding MLL associated leukemia, which provide unforeseen opportunities to overcome this dreadful illness. Nevertheless, much needs to be learned about the normal biology and pathology of MLL and MLL fusions. For instance, although MLL fusions play an indispensable role in the MLL leukemogenesis, data support the necessity of additional complementary mutations to initiate a full MLL leukemia phenotype. The presence of a second hit has been implicated in MLL-AF4, MLL-AF9, MLL-CBP and MLL-lacZ knock-in models where engineered mice only developed leukemias after a long latency or a challenge with carcinogens such as ENU or γ -irradiation.^{57,59,70,72} Indeed, several reports have identified mutations of *p53*, *ATM*, *Ras* and *Flt3* in MLL leukemia patients.^{97,106-109} Furthermore, an interesting feature of human MLL leukemia is its relatively short latency, which implies a rapid acquisition of necessary additional mutations. Therefore, an underlying DNA damage checkpoint defect in MLL leukemia has been proposed based on an in vitro cell culture system. It was demonstrated that a functional activation of MLL-ENL enhances chromosomal aberrations, indicating a DNA damage checkpoint defect.¹¹⁰ Furthermore, leukemic cells bearing MLL-ENL are resistant to chemotherapy due to an attenuated p53 response.¹¹¹ The importance of checkpoint compromise, including but not limited to the deregulation of p53, in MLL fusion leukemogenesis warrants future scrutiny and validation.

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